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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/859,722	05/17/2001	William Stuart Somers	16163-004001 / AM100225	2770

26169 7590 07/03/2006

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EXAMINER	
NOAKES, SUZANNE MARIE	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 07/03/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/859,722	SOMERS ET AL.	
	Examiner	Art Unit	
	Suzanne M. Noakes, Ph.D.	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15,16 and 36-60* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15,16 and 36-60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 May 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/10/01, 8/19/04*. 1-3-06
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *IDS 1-3-06; Appendix A*.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group VIII, claim 15, in the reply filed on 26 April 2006 is acknowledged. The traversal is on the ground(s) that the separation of claims 15 and claims 16 into Groups VIII and IX, respectively, are not unrelated subject matter and should be rejoined and examined together. Upon reconsideration, the examiner finds Applicants arguments persuasive and claim 16 will be rejoined with claim 15, Group VIII.

The restriction requirement, however, is still deemed proper and is therefore made FINAL.

Status of the Application

2. The amendments to the claims and remarks filed 26 April 2006 are acknowledged. Claims 1-14 and 17-35 have been cancelled. Claim 36-60 have been added. Claims 15, 16 and 36-60 are pending and subject to examination.

Information Disclosure Statement

3. The information disclosure statement (IDS) submitted on 10 December 2001, 19 August 2004 and 03 January 2006 have been considered by the examiner. See signed and attached PTO-1449.

The reference of Thakker et al., cited on the IDS of 10 December 2001 has not been considered as there is no copy of the reference in the file.

Drawings

4. The drawings are objected to because Figures 2-5 should have some sort of identifier at the start of each table detailing the contents of the .pdb coordinates, the sequence of the protein (e.g. a SEQ ID No:) represented by the three-dimensional structural coordinates, the space group and unit cell parameters and number of molecules per asymmetric unit. An ideal example of the required information would either be a scaled down version or the same header information required by the RCSB protein data bank and the information found in the header section of each deposit (see www.rcsb.org/pdb/). Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Compliance with the Sequence Rules

5. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequence set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. § 1.821 through 1.825; applicants' attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990) and 1114 OG 29 (May 15, 1990).

a) The structural coordinates in Figure 2, 3 and 5, i.e., chain/molecule A, B, C and D, teach several amino acid sequences since a particular amino acid is assigned to a linear sequence in a particular order. As such, the amino acid sequence disclosed within the atomic coordinates must comply with the sequence rules. Labeling using a SEQ ID NO must be inserted into the brief description of the drawings or into the Figure directly.

If the noted sequences are in the sequence listing as filed, Applicants must amend the specification to identify the sequences appropriately by SEQ ID NO. If the noted sequences are not in the sequence listing as filed, Applicants must provide (1) a substitute copy of the sequence listing in both computer readable form (CRF) and paper copy, (2) an amendment directing its entry into the specification, (3) a statement that the content of the paper and CRF copies are the same and, where applicable, include no new matter as required by 37 C.F.R. § 1.821 (e) or 1.821(f) or 1.821(g) or 1.821(b) or 1.825(d), and (4) any amendment to the specification to identify the sequences appropriately by SEQ ID NO.

Specification

6. The disclosure is objected to because of the following informalities: The Brief Description of the Drawings for Figures 2-5 does not make it very clear how many molecules per asymmetric unit exist and have been refined. For instance, Figures 2 and 3 each have four molecules per asymmetric unit whereas Figure 5 has only two and Figure 4 has only one. Because the figures are so lengthy, this information would be helpful in the descriptions.

Appropriate correction is required.

Claim Objections

7. Claims 39, 40 and 45-48 objected to because of the following informalities: The claim is drawn to specific amino acids of Figure 3 that define an active site of P-selectin LE; one of the residues identified is ASN106 (asparagine 106). There is no ASN106 P-selectin LE, rather amino acid 106 is an aspartate. Appropriate correction is required.

Claim Rejections - 35 USC § 101

8. 35 U.S.C. 101 reads as follows:

> **Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.**

9. Claims 15, 16 and 36-60 are rejected under 35 U.S.C. 101 because the claimed invention lacks patentable utility.

The methods are drawn to an *in silico* screening method to identify an agent which interacts with P-selectin LE by utilizing known computer programs/algorithms to

screen for agents that can interact with the novel three-dimensional coordinates. The instant claimed methods utilize *in silico* method steps.

The methods are deemed to be statutory subject matter because the claimed invention does have a practical application because the method provides a useful, concrete and tangible result which is that it can be used as a guide for further screening. This is the requirement and analysis for statutory subject matter under State Street Bank & Trust Co. rationale (see *State Street Bank & Trust Co. v Signature Financial Group Inc.*, 149 F.3d 136B, 1373, 47 USPQ2d 1596, 1601-02 (Fed. Cir. 1998), and the analysis setout by the USPTO in case 6 of the Trilateral Project WM4, Annex 3 - USPTO analysis of claims 1-3, p. 71, paragraph A1. However, determination of statutory subject matter versus the determination of patentable utility are distinct inquires.

Utility in this case does not depend upon the utility of the claimed methods but rather it depends on the utility of the candidate compounds identified as a result of the screening methods.

As stated *supra* the claims are drawn to a method of identifying an agent that interacts with P-selectin by performing *in silico* screening methods. The specification teaches that selectins are glycoproteins that are responsible for early adhesion events in the recruitment of leukocytes into sites of inflammation and their emigration into lymphatic tissues. Specifically, P-selectins are induced on the vascular endothelium in response to inflammatory stimuli and also are produced by activated platelets. All selectins possesses several different domains (see p. 2, lines 5-10); P-selectin LE and

structural coordinates thereof are just two domains out of the whole protein where the calcium binding lectin domain (L) and the epidermal growth factor (EGF)-like domain (e) are the focus of the claimed invention (Figures 2, 3 and 5). It is further taught that the P-selectin LE domain is capable of binding a functional peptide PSGL-1, calcium and sialyl Lewis^x tetrasaccharide (SLe^x), all of which bind in the lectin domain. Distinct three-dimensional binding and activation sites in the lectin domain are disclosed (see p. 7, lines 4-17 and p. 8, lines 3-18). The specification also states on p. 10, lines 21-25, "The present invention provides agents, activators or inhibitors identified using the foregoing methods [*in silico* screening methods]. Small molecules or other agents which inhibit or interfere with the selectin-mediated cellular rolling of leukocytes over vascular tissue may be useful in the treatment of diseases involving abnormal inflammatory responses such as asthma and psoriasis."

However, despite considerable detail of the selectins and the identification of specific interaction sites identified by three-dimensional structures complexed with ligands (Figures 3 and 5), the specification fails to specifically detail the specific utility for the compounds that are being identified in the method claims and merely skirts around the issue by identifying *potential* uses of the compounds; however, these potential uses may constitute false prophecies. The claims are strictly directed to identification of molecules which interact with P-selectin but exactly what constitutes an 'interaction', how much interaction needs to be present (e.g. covalent bonding, weak hydrogen bonding etc.) and what is to be achieved as a result of said interaction is not addressed anywhere. The specification identifies what inhibitors might be used for, but

for instance, what if the identified compound is an activator or does merely interact with no modulation to the P-selectin activity. These compounds do fall within the scope of the instant claims and invention but do not have a specific, substantial or credible utility. The deficiency in the identification of what the interacting compounds identified by the claimed invention actually are to be used for necessitates the rejection of non-utility because the examiner, the skilled artisan and the general public are left only with non-existent/prophetic ideas.

Thus, in the absence of a disclosed correlation between the interaction of an agent with P-selectin and some sort of modulation (e.g. activation, inhibition, etc.) resulting from said interaction and the actual intended use of the compounds identified, merely identifying compounds which may interact with protein P-selectin LE is not a specific, substantial, and credible utility. (See case 6 of the Trilateral Project WM4, USPTO analysis of claims 1-3, p. 71, paragraph A2).

10. Claims 15, 16 and 36-60 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific, substantial and credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claim Rejections - 35 USC § 112 –2nd paragraph

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 15, 16 and 36-60 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims are deemed indefinite for the recitation "employing said three-dimensional model to design or select an agent" as it is unclear as to how the 3-D structure is "employed" in the design or selection.

13. Claims 15, 16 and 36-60 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as their invention. The claims are rendered indefinite because the metes and bounds of the term "relative structural coordinates" are not defined in the claims or in the specification and it is unclear to those skilled within the art. For instance, could a skilled artisan, use a homology model, NMR structure or x-ray structure coordinates of another selectin, that happen to be less than 1.5Å rmsd to Figs. 2, 3 and 5 and use these in the instant claimed invention since these are "relative structural coordinates" and still be within the scope of the claimed invention? Maybe, but maybe not. As such there is no way to determine the scope to which patentability is sought.

14. Claim 16 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: a step that actually measures or assays something, e.g. activation, inhibition, modulation or something that identifies that interaction between the identified compound and P-selectin LE has occurred.

15. Claim 37 recites the limitation "the method of claim 15, wherein obtaining the agent comprises synthesizing the agent" in reference to the *in silico* method described in claim 15. There is insufficient antecedent basis for this limitation in the claim because the method of claim 15 does not involve obtaining the agent, rather it identifies the agent. There is no actual physical 'real world' action performed in claim 15 as claim 37 suggests.

Claim Rejections - 35 USC § 103

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

17. The following excerpt is from MPEP § 2106 section VI "DETERMINE WHETHER THE CLAIMED INVENTION COMPLIES WITH 35 U.S.C. 102 AND 103" and is applied to the below 35 USC §103(a) rejection wherein the claimed limitations of "generating a three dimensional model of P-selectin LE using the relative structure coordinates of Figures 2, 3 and 5 ± 1.5Å" and "...wherein the active site comprises relative structural coordinates of amino acids ....." are considered "non-functional descriptive material".

> As is the case for inventions in any field of technology, assessment of a claimed computer-related invention for compliance with 35 U.S.C. 102 and 103 begins with a comparison of the claimed subject matter to what is known in the prior art. If no differences are found between the claimed invention and the prior art, the claimed invention lacks novelty and is to be rejected by Office personnel under

35 U.S.C. 102. Once distinctions are identified between the claimed invention and the prior art, those distinctions must be assessed and resolved in light of the knowledge possessed by a person of ordinary skill in the art. Against this backdrop, one must determine whether the invention would have been obvious at the time the invention was made. If not, the claimed invention satisfies 35 U.S.C. 103. Factors and considerations dictated by law governing 35 U.S.C. 103 apply without modification to computer-related inventions.

If the difference between the prior art and the claimed invention is limited to descriptive material stored on or employed by a machine, Office personnel must determine whether the descriptive material is functional descriptive material or nonfunctional descriptive material, as described supra in sections IV.B.1(a) and IV. B.1(b). Functional descriptive material is a limitation in the claim and must be considered and addressed in assessing patentability under 35 U.S.C. 103. Thus, a rejection of the claim as a whole under 35 U.S.C. 103 is inappropriate unless the functional descriptive material would have been suggested by the prior art. > In re Dembiczak, 175 F.3d 994, 1000, 50 USPQ2d 1614, 1618 (Fed. Cir. 1999).< Nonfunctional descriptive material cannot render nonobvious an invention that would have otherwise been obvious. Cf. In re Gulack, 703 F.2d 1381, 1385, 217 USPQ 401, 404 (Fed. Cir. 1983) (when descriptive material is not functionally related to the substrate, the descriptive material will not distinguish the invention from the prior art in terms of patentability).

Common situations involving nonfunctional descriptive material are:
- a computer-readable storage medium that differs from the prior art solely with respect to nonfunctional descriptive material, such as music or a literary work, encoded on the medium,

- a computer that differs from the prior art solely with respect to nonfunctional descriptive material that cannot alter how the machine functions (i.e., the descriptive material does not reconfigure the computer), or

- a process that differs from the prior art only with respect to nonfunctional descriptive material that cannot alter how the process steps are to be performed to achieve the utility of the invention.

Thus, if the prior art suggests storing a song on a disk, merely choosing a particular song to store on the disk would be presumed to be well within the level of ordinary skill in the art at the time the invention was made. The difference between the prior art and the claimed invention is simply a rearrangement of nonfunctional descriptive material.

18. Claims 15 and 36-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Revelle et al. (JBC, 1996, 271(27):16160-16170 – cited on the IDS from 10 December 2001) in view of Morris et al. (J. of Computer-Aided Molecular Design. 1996. Vol. 10, pp. 293-304) in view of *In re Gulack* 217 USPQ 401 (Fed. Cir. 1983) and *In re Ngai* 70 USPQ2d 1862 (Fed. Cir. 2004). See MPEP §§ 2144 and 2144.04 regarding legal precedent as a source of rationale for rejection under 35 U.S.C. § 103.

All claim limitations concerning the machine readable data comprising structure coordinate data of Figures 2, 3 and 5 are given no patentable weight as it is considered to be non-functional descriptive material. As such, the instant claims are considered to be limited to a method of using a known computer program to identify agents that interact with P-selectin by inputing the three-dimensional structural coordinates into said computer program, and analyzing the output by visual/mental interpretation.

Revelle et al. teach that E-selectin and P-selectin are two closely related vascular cell adhesion proteins, each with a lectin type domain that binds carbohydrates and a EGF-like domain (see first two lines of Abstract). Revelle et al. also teach site directed mutataions of both proteins leading to structural and functional insights to the mode of action of selectins. Exactly how the mutations actually lead to their role in the disruption of selectin activity is unclear. It is specifically stated, that it seems likely that only the three-dimensional structure (NMR or protein crystallography) will be able to elucidate the mechanism of action of the selectins. Furthermore, "the presented data do offer new insight into selectin/ligand interactions and perhaps identify the necessity for further structural and functional analyses of those interactions and their modulation. It is hope

that this information will aid in the design and identification of high affinity selectin inhibitors that may be used for the treatment of selectin-mediated inflammatory disease." (see p. 16170, 1st column, last four sentences). Revelle et al. do not, however, teach the three-dimensional structure or the *in silico* design and identification of inhibitors of P-selectin.

Morris et al. sets forth a software program developed for designing and determining the potential ligand-protein interactions based on known protein structures (AutoDock). The program aids the skilled artisan in determining if a protein ligand specifically interacts with the known protein structure and how well/likely said interaction actually is. The user interface requires that the skilled artisan provide the three-dimensional structure file (also known as the .pdb file) as determined by X-ray crystallographic, solution NMR spectroscopy or other known means. The disclosed program includes a full description of an advanced software system specifically for performing simulated annealing and rigid body refinement of the protein with the potential bound ligand. The program thus gives a more accurate analysis of the energy minimum/maximum calculations required for 'real world' ligand-protein interaction (e.g. the likely-hood of ligand interacting in a non-static protein) [see Introduction, p. 293]. It is taught on p. 293, 2nd column, 1st full paragraph, that the program has been used successfully in the prediction of substrates binding to enzymes and computer-aided drug design of non-peptide inhibitors as well as other applications. The suite of software for AutoDock quite simply can be manipulated by different commands by the user in order to produce the results desired so long as the protein structure is known.

Revelle et al. teach why a skilled artisan would be motivated to investigate the interaction of ligands with either P-selectin or E-selectin: because the design and identification of high affinity selectin inhibitors may be used for the treatment of selectin-mediated inflammatory disease. Morris et al. teach a computer program that specifically is used with structural coordinates/data that are fed into a known algorithm whereby the program identifies interactions between the structural coordinates and a known or designed ligand. The computer program uses a series of pre-defined processing steps in order to identify the interaction and the data which is input into the program do not intrinsically impose a change to those processing steps and are thus the data is nonfunctional descriptive material. In *Gulack* and *Ngai*, the respective Courts held that nonfunctional descriptive material cannot render nonobvious an invention that would have otherwise been obvious. In the instant case, a method of using a known computer program (such as those listed on p. 23 of the specification or that of Morris et al.) for its known and intended purpose to compare data and ligand interaction does not become nonobvious merely because new structural data becomes available for analysis.

Therefore it would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains to utilize the program AutoDock (developed by Morris et al.) which is specifically used for identifying agents/ligands that interact with macromolecular structures and to use said program with any three-dimensional structural coordinates, including those of the instant claims/invention.

19. Claims 15, 16 and 36-60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Graves et al. (Nature, 1994, Vol. 367, pp. 532-538) in view of Morris et al. (cited above) and as evidenced by the root-mean square deviation (rmsd) comparisons of the three-dimensional structural coordinates of Figures 2, 3 and 5 with that of the three-dimensional structural coordinates of Graves et al. (pdb accession code:1ESL).

The claims are drawn to *in silico* methods of identifying agents that interact with P-selectin LE based on the structural coordinates of Figures 2, 3 and 5. Figure 2 is the three-dimensional coordinates of P-selectin that has only the lectin domain and the EGF domain and 4 molecules per asymmetric unit, where each molecule contains 158 total amino acids. Figure 3 is the three-dimensional coordinates of P-selectin that has only the lectin domain and the EGF domain and 4 molecules per asymmetric unit, where each molecule contains 158 total amino acids, and also has the carbohydrate structure sialyl Lewis X (Sle^x) bound to the lectin domain. Figure 5 is the three-dimensional coordinates of P-selectin that has only the lectin domain and the EGF domain and 2 molecules per asymmetric unit, where each molecule contains 158 total amino acids, and the peptide PSGL-1 is bound to the lectin domain. The primary amino acid sequence located in each P-selectin molecule is found in Figure 6A; the entire P-selectin protein sequence is listed and the amino acids present in each molecule (e.g. the amino acids in the lectin and EGF-domain) are underlined.

Graves et al. teach the X-ray crystal structure/three-dimensional coordinates of the lectin domain and the EGF domain of E-selectin (E-selectin LE). The coordinates

have been refined with 157 visible amino acids, one molecule per asymmetric unit and to an overall resolution of 2.0 Å. Graves et al. also teach that there are three members of the selectin gene family: E, P and L, and that the selectins constitute a highly conserved gene family sharing a common structural organization and function during inflammation. Each selectin contains an N-terminal lectin domain followed by an epidermal growth factor-like element (EGF) and other common and similar domains. It is also taught that *all* selectins can bind the carbohydrate Sle^x (see p. 532, 1st column, 1st paragraph). Thus, it is taught that E-selectin, P-selectin and even L-selectin will share common ligand interaction sites. Graves et al. also teach that since the E-selectin ligand binding domains are now known that this now provides opportunities for the design of compounds to regulate the accumulation of leukocytes at sites of inflammation (all selectins are involved in this process) see last line, p. 536. Graves et al., however, do not teach the three-dimensional structure of P-selectin ands methods of identifying agents that interact with P-selectin.

The teachings of Morris et al. are described above. Briefly, Morris et al. teach a computer software programs (AutoDock) that is used by skilled artisans in order to identify ligands or agents which will interact with a known protein structure. A user must input the structural coordinates and ligand(s) (or use a database of known ligands) in order to identify if the ligand/agent interacts with the protein structure.

Applicants specification on p. 15 specifically define the use of "structural coordinates" and their applicability to the instant application. It is clearly identified that structural coordinates can be obtained using NMR, homology modeling, x-ray

crystallography etc. Furthermore, the structural coordinates of the instant invention of Figures 2-5 can be modified by mathematical manipulation and as such, the structural coordinates of the present invention are relative, "and are in no way specifically limited by the actual x, y, z, coordinates of Figures 2, 3, 4 and 5". (see p. 15, lines 7-19).

Therefore it would have been obvious to one of ordinary skill in the art at the time the invention was made to use Graves' et al. E-selectin LE three-dimensional protein structure and use it in Morris et al. AutoDock program in order to identify ligands/agents that will interact with P-selectin. It would be obvious to use E-selectin LE in lieu of P-selectin LE because the three-dimensional structure was known, and Graves et al. teach that the selectin family is highly homologous (both structurally and functionally). Also it is taught that all selectins have at least one ligand in common, that being Sle^x, and that all selectins have lectin and EGF domains which make up their ligand binding domains. (This fact is also evidenced by Applicants own work that shows Sle^x bound to P-selectin (Figure 3) and E-selectin:Sle^x complex (Figure 4)). Furthermore, the claim limitations specifically state that the generated three-dimensional structural model is not more than 1.5Å root-mean square deviation from the backbone atoms of Figures 2, 3 and 5 and Applicants state that their invention is in no way limited to the actual structural coordinates presented in Figures 2, 3 and 5. It is known to a skilled artisan that when comparing structures, those having less than 1.5Å rmsd (overall) of carbon-atom backbones will be a highly homologous structure (see Brenden et al., p. 249, Figure 16.1). In the instant case, when the structural coordinates of E-selectin LE from Graves et al. (pdb:1ESL) is applied to a rotation and translation matrix via the computer

program Dali and compared to Figures 2, 3 and 5 of the instant application, each molecule from each structure/Figure (e.g. E-selectin compared to all four molecules of each Figures 2, 3 and 5) has a rmsd of 0.6-0.8Å (see the output by Dali – Appendix A). Thus, when utilizing E-selectin in the claimed methods rather than P-selectin there would be a large expectation of success given that "the selectins are a highly conserved gene family sharing common structural organization" (see Graves, p. 532, 1st column, 3rd line) and that their rmsd is so low. Furthermore, motivation to identify ligands that interact with any of the selectins will provide significant insight into selectin interaction and how they recruit leukocytes to the sites of inflammation (see last line of Abstract, Graves et al., p. 532). Testing of the identified compounds *in vitro* or *in vivo* would be the obvious next step in order to see if the newly designed or identified compounds are indeed able to regulate the accumulation of leukocytes at sites of inflammation as suggested by Graves et al. (see last line, p. 536).

In light of teachings described above, it therefore would have been *prima facie* obvious to use the structural coordinates as defined by Graves et al. E-selectin LE in a method to identify compounds that will interact with P-selectin (or any selectin for that matter) by utilizing the E-selectin LE structural coordinates with Morris' et al. AutoDock program, and to have a high expectation of success in identifying compounds that interact with P-selectin LE successfully because the two selectins are so highly homolgous, both structurally and functionally.

Conclusion

20. In the absence of any recitation of an intended use for the compounds identified which will interact with P-selectin LE, the claims are considered not possess any utility under 35 U.S.C. § 101. Nonetheless, the claims are considered obvious in light of *In re* Gulack and Morris et al. because the non-functional descriptive material does not materially change the AutoDock program of Morris et al. and the outcome of what the program was originally intended to be used for, e.g. identification of protein-ligand interactions. Finally, the claims are also deemed obvious because the three-dimensional protein structure of E-selectin LE is known and actually are so highly homologous with P-selectin LE that identification of ligands that interact with E-selectin LE will likely result in the identification of compounds that also interact with P-selectin LE.

Therefore, no claim is allowed.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Suzanne M. Noakes, Ph.D. whose telephone number is 571-272-2924. The examiner can normally be reached on Monday to Friday, 7.30am to 4.00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber or Kathleen Kerr can be reached on 571-272-0925 and 571-272-0931, respectively. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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SMN
07 June 2006

Jon Weber
Supervisory Patent Examiner